



## Recombinant Human Platelet-Derived Growth Factor- $\beta\beta$ (rhPDGF- $\beta\beta$ )

LT Vinh T. Ton, DC, USN and Commander Ivan Roman, DC, USN

### Introduction

Growth factors are proteins that have the ability to stimulate cell growth, proliferation and differentiation. Discovered in 1974, Platelet Derived Growth Factor (PDGF) is stored in the alpha granules of platelets and also produced by osteoblasts, macrophages and monocytes. Three different isomers of PDGF exist: PDGF- $\alpha\alpha$ , PDGF- $\beta\beta$ , and PDGF- $\alpha\beta$  (1). PDGF- $\beta\beta$  has chemotactic and mitogenic effects on periodontal mesenchymal stem cells (2), cementoblasts (3), periodontal ligament (PDL) fibroblasts (4) and osteoblasts (5). Because of these properties PDGF- $\beta\beta$  has been investigated as a potential biologic material to aid in periodontal soft and hard tissue regeneration. PDGF can be extracted from the patient by centrifugation of their whole blood to obtain platelet rich plasma (PRP) (6). Activation of the platelets in PRP releases the PDGFs. Procuring PDGF in this manner has limitations. The number of platelets (and consequently PDGF- $\beta\beta$  levels) in PRP varies depending on the procurement method (1), it is time consuming, additional equipment increases expense, and requires a phlebotomy. Recombinant human PDGF- $\beta\beta$  (rhPDGF- $\beta\beta$ ) now commercially available can be produced in unlimited quantities, contains pure and consistent concentrations of the protein, reduces need for additional equipment and does not require a phlebotomy. The purpose of this clinical update is to review the biological properties of rhPDGF- $\beta\beta$  and its possible clinical applications.

### Biological properties of rhPDGF- $\beta\beta$

#### Role of rhPDGF- $\beta\beta$ in periodontal ligament (PDL) fibroblast and gingival fibroblast (GF) cells

PDL fibroblasts are thought to be key cells in periodontal regeneration (7) and are in competition with gingival fibroblasts (GF) (having less regenerative potential) in repopulating denuded root surfaces due to periodontal disease. In vitro, PDGF- $\beta\beta$  has positive chemotactic and mitogenic effects on PDL fibroblasts. In contrast PDGF- $\beta\beta$  has a negative or inhibitory mitogenic effect on GF (4). Zaman et al. reported higher PDL fibroblast proliferation on the root surfaces treated with rhPDGF- $\beta\beta$  versus non-rhPDGF- $\beta\beta$  treated control groups (8). When combined with bone allograft Demineralized-Freeze Dried Bone Allograft (DFDBA) or Freeze-Dried Bone Allograft (FDBA), rhPDGF- $\beta\beta$  has also been shown to induce higher PDL fibroblast proliferation as compared to DFDBA or FDBA alone in vitro (9).

#### Role of rhPDGF- $\beta\beta$ in osteogenesis

In vivo studies have demonstrated that the use of rhPDGF- $\beta\beta$  in the treatment of intrabony defects results in higher turnover and more new bone formation during healing. Sarment et al. measured the amount of pyridinoline crosslinked carboxyterminal telopeptide of type I collagen (ICTP), a bone turnover biomarker to measure new bone formation (NBF), in the treatment of chronic diseased periodontal defects over a 24 week period using rhPDGF- $\beta\beta$ . Results showed that rhPDGF- $\beta\beta$  treated sites had a significantly higher amount of ICTP released (higher new bone formation)

locally for up to six weeks compared to the alloplast treated group (10).

### Clinical applications of rhPDGF- $\beta\beta$

Thus far, rhPDGF- $\beta\beta$  has been used successfully in combination with a variety of periodontal therapies including guided tissue regeneration (GTR) (11, 12), guided bone regeneration (GBR) (13, 14, 15), block graft augmentation (16), root coverage (17), and sinus lift procedures (18).

#### Guided tissue regeneration procedures

In vivo studies have demonstrated that rhPDGF- $\beta\beta$  with particulate graft material enhances the clinical outcomes and promotes early wound healing of periodontal regeneration procedures in intrabony and furcation defects (11, 12, 19, 20). Histological analysis of periodontal defects treated with rhPDGF- $\beta\beta$  and particulate graft has shown evidence of periodontal regeneration (formation of new cementum, PDL, and bone) with no evidence of root resorption, ankylosis, inflammation, or adverse tissue responses (11, 12, 21). Nevins et al. compared the pocket depth (PD) reduction and clinical attachment level (CAL) gain in intrabony and furcation defects treated with bone graft (DFDBA or xenograft) and rhPDGF- $\beta\beta$  (test) vs. bone graft (DFDBA or xenograft) and collagen membrane (control). They reported that the average PD reduction and CAL gain in test and control groups at 9 months were 6.42 mm and 6.17 mm respectively (12). In a two patient case series with re-entry Nevins et al. reported that rhPDGF- $\beta\beta$  in combination with FDBA resulted in an average 7mm PD reduction and 6.5 mm CAL gain (22). Rosen et al. obtained a mean reduction in PD of 3 mm and a CAL gain of 4.1 mm when using rhPDGF- $\beta\beta$  in combination with FDBA and a bioabsorbable collagen wound healing dressing (Collatape™) (20).

#### Ridge augmentation procedures

The use of rhPDGF- $\beta\beta$  with DFDBA or FDBA for ridge augmentation has been limited. In a three case series Nevins et al. showed excellent results with the use of rhPDGF- $\beta\beta$  with DFDBA or FDBA and a collagen membrane (13). Nevins et al. also used rhPDGF- $\beta\beta$  and mineral collagen bone substitute (MCBS) without the use of any membranes for buccal plate regeneration and observed that it provided the best ridge morphology for implant placement when compared to those obtained with MCBS alone, MCBS with enamel matrix derivatives (EMD) and bone ceramic with EMD (14). In a case report, Simion et al. demonstrated that adding rhPDGF- $\beta\beta$  to a xenograft and autogenous bone graft combination resulted in the restoration of a large defect of approximately 20 mm (15). In an animal study, the new bone regenerated from xenograft block grafting in combination with rhPDGF- $\beta\beta$  appeared to display similar composition, structure and physical properties to those of native bone (16).

## Periodontal plastic procedures

RhPDGF- $\beta\beta$  can be used effectively in the treatment of gingival recession defects (GRDs). McGuire et al. measured CAL and percentage of root coverage (%RC) gains in two groups: rhPDGF- $\beta\beta$  + Collatape™ + ( $\beta$ -TCP) as test group and connective tissue grafts (CTGs) as the control group in the treatment of GRDs. They reported that CAL and %RC gains were 2.9 mm and 91% in the test group compared to 3.5mm and 99% in the control group, respectively (17). Although the connective tissue graft was statistically significantly superior in obtaining a higher %RC the use of Collatape™ with rhPDGF- $\beta\beta$  and  $\beta$ -TCP does not involve a donor site and could be considered an alternative treatment to connective tissue grafts on patients with GRDs.

## Sinus lift procedures

A sinus lift is performed by placing bone or bone substitute materials underneath the Schneiderian membrane to increase available bone in preparation for implant placement. The recommended minimum healing time to predictably place an implant in a sinus augmented site is usually 4-10 months depending on the amount of native bone at the time of augmentation (23). Scheyer et al. performed sinus lifts on two patients with remaining native alveolar bone heights of <1mm and 3 mm respectively with a mixture of rhPDGF- $\beta\beta$  and bovine xenograft. Implants were placed at only 3.5-4.5 months post-grafting, restored 4 months later, and were successful 2.4-3 years later. In addition, histology showed significant amounts of vital bone being formed as early as 3.5 months (18). Although more research seems prudent, adding rhPDGF- $\beta\beta$  to the bone graft material during sinus augmentation may accelerate bone formation, allowing earlier implant placement in the severely pneumatized sinus, and provide long term successful results (18).

## **How supplied? How to use it?**

RhPDGF- $\beta\beta$  is sold under the brand name GEM21S® and must be refrigerated at 2-8°C (36-46°F) during storage (24). The product is currently approved by the Food and Drug Administration (FDA) for treatment of intrabony defects, recession, and furcation defects only. Each GEM21S® kit contains one syringe filled with 0.5ml (0.3mg/ml) rhPDGF- $\beta\beta$  and 0.5 cc of  $\beta$ -TCP alloplast particles. Off-label use of rhPDGF- $\beta\beta$  with other particulate grafting material besides  $\beta$ -TCP has been demonstrated clinically efficacious (12, 14, 20). It is recommended that particulate grafting material be fully hydrated by saturating the particles with the rhPDGF- $\beta\beta$  solution for a minimum of 10 minutes before use (24).

## **Safety**

RhPDGF- $\beta\beta$  is safe and effective in the treatment of periodontal defects (11, 12, 14). There have been no side effects reported in short and long term follow-up of cases (19, 25).

## **Conclusion**

Although more research is needed the biochemical properties and potential for accelerating healing make rhPDGF- $\beta\beta$  an ideal biologic material to be considered as an important armamentarium in periodontal surgical therapy.

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Lieutenant Ton is a 3rd year Periodontics Resident and CDR Roman is Program Director of Periodontics, Naval Postgraduate Dental School, Navy Medicine Professional Development Center, Bethesda, MD.

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